REMARKS/ARGUMENTS

Claims 1-11 are pending in the above-identified application. Claims 1 and 2 are amended as set forth in detail herein. Support for these amendments is identified in the following remarks. No new matter has been added by these amendments. Examination and reconsideration of all pending claims are respectfully requested.

Rejections under 35 USC § 112, first paragraph

Claims 1-11 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly not enabled by the specification as filed. The Examiner's bases for maintaining this rejection appear to be threefold. First, the Examiner contends that ES cells are not broadly enabled with respect to animals other than mouse. Second, the Examiner states that the claims encompass administration of xenogeneic cells and that the "specification does not teach that any thymocyte or any isolated multipotent cell, with or without $p27^{Kip1}$ gene are sufficient to overcome the immune system mediated hyperacute rejection of xenogeneic tissues due to differences in surface carbohydrate moieties among different species." Finally, the Examiner continues to rely on Miller and Vile (*FASEB J.* 9:190-199, 1995) as allegedly raising an issue with respect to gene delivery.

With respect to the first alleged basis for rejection (scope of ES cells), while Applicants do not agree nor acquiesce to the rejection for at least the reasons of record, but in order to further expedite prosecution of the instant application, Applicants have amended independent claim 1 to recite, *inter alia*, "altering an endogenous gene encoding $p27^{Kip1}$ in an isolated thymocyte, or an isolated ~~multipotent~~ hematopoietic cell that differentiates into a thymocyte ...." A corresponding amendment has also been made to dependent claim 2. Support for these amendments is found in the specification at, *e.g.*, page 5, lines 14-26. In view of these amendments, the aspect of the Examiner's rejection on the basis that "multipotent cell" encompasses ES cells is obviated.

With regard to the Examiner's second alleged basis for rejection (alleged non-enablement of administration of xenogeneic cells), Applicants respectfully note that the presence of inoperative embodiments within the scope of a claim does not render a claim nonenabled where one of skill in the art would readily understand which embodiments would be inoperative or operative with expenditure of no more effort than is normally required in the art. MPEP § 2164.08(b). It is submitted that xenogeneic transplant rejection is a factor well-understood in the art and, therefore, that the skilled artisan would readily understand whether such an embodiment is inoperative or operative (*e.g.*, with use of immunodeficient transplant recipients such as, for example, NOD/SCID mice) without any undue experimentation.

Finally, with regard to the Miller reference, Applicants respectfully note that, because the claims recite altering an endogenous $p27^{Kip1}$ gene in an isolated thymocyte, or an isolated hematopoietic progenitor, the claims are directed to, *inter alia*, a method of gene delivery *ex vivo*. Applicants further note that any issues discussed in Miller with respect to gene delivery are primarily in the context of the targeting of specific cell populations or tissues *in vivo*, an issue that is not relevant to introduction of a gene into a cell *ex vivo*, as presently claimed. (*See, e.g.*, Miller at page 197, second column, last paragraph, stating that with "ex vivo manipulation of target cells ... the vector requires very little, if any, intrinsic targeting capability").

For at least the reasons set forth above, Applicants believe the present claims to be enabled by the specification as filed. Withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. § 102

Claims 1-11 stand rejected under 35 U.S.C. 102(e) as allegedly anticipated by Roberts *et al.* (U.S. Patent No. 5,958,769, dated 8-28-1999, filing date 1-18-1996).

While Applicants do not believe that the present invention is anticipated by Roberts *et al.*, but in order to further expedite prosecution of the instant application, Applicants have amended claim 1 to recite the step of "monitoring the animal to detect the increase in

thymocyte proliferation." Support for this amendment is found in the specification as filed at, for example, page 31, line 29, to page 33, line 30.

The Examiner has not shown where Roberts *et al.* disclose the detection of thymocyte proliferation in an animal. In this regard, Applicants respectfully refer the Examiner to columns 19 and 20 of Roberts *et al.*, which describe analysis of the size difference of internal organs, including thymus, between normal and p27 knockout mice. (*See* col. 19, l. 26, to col. 20, l. 8.) While counts of "nucleated cells" from the thymus were performed, proliferation of thymocytes was not assayed.

Accordingly, in light of the present amendment to independent claim 1, Applicants believe the present rejection of claims 1-11 under 35 U.S.C. § 102 to be obviated. Applicants therefore believe that a Declaration under 37 CFR § 1.131 is no longer required with respect to the rejection. Withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-467-9600.

Respectfully submitted,

Dated: October 19, 2005

By: _____
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